PATENT COOPERATION TREATY

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PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/012087	International filing date *(day/month/year)* 15.10.2004
Priority date *(day/month/year)* 15.10.2003	
International Patent Classification (IPC) or both national classification and IPC A61K39/00, C07K14/47, C12N15/12, C12N5/10, C07K16/30, G01N33/574	
Applicant ISTITUTO SUPERIORE DI SANITÀ	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/012087

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 21-26 (as to I.A.)

because:

☒ the said international application, or the said claims Nos. 21-26 (as to I.A.) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10,15-18,21-29
	No:	Claims	11-14,19,20
Inventive step (IS)	Yes:	Claims	8-10,17,18,22-24
	No:	Claims	1-7,15,16,19-21,25-29
Industrial applicability (IA)	Yes:	Claims	1-20,27-29
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item II

Priority

Should the priority date of the present application turn out not to be valid, then document D1 would become relevant in the context of novelty and inventive step.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 21-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1: MACCALLI CRISTINA ET AL: "Identification of a colorectal tumor-associated antigen (COA-1) recognized by CD4+ T lymphocytes." CANCER RESEARCH, vol. 63, no. 20, 15 October 2003 (2003-10-15), pages 6735-6743 ISSN: 0008-5472

D2: SMITH COROLINE ET AL. (2002) British Medical Bulletin 64:181-200

D3: WO2003050253

2 **Preliminary Remarks**

2.1 In order to assess novelty (Art. 33(2) PCT) and inventive step (Art. 33(3) PCT) the attention of the applicant is drawn to following remarks:

2.2 Second medical use claim 1 is not acceptable under Art.6 PCT since the therapeutic application is not defined in the form of a real treatment of a pathological condition (disease). The claim is therefore being interpreted as referring to the use to stimulate an immune response against colorectal cancer (claim 6) and melanoma (claim 29) cells.

2.3 The subject-matter of claim 12 refers to a peptide defined in claims 2-5. These claims

however do not define a peptide, but its use as immunogen. Present claim 12 therefore is unclear and lacks any technical feature to define the peptide (Art.6 PCT). However, since the subject-matter of claims 2-5 comprises the definition of a peptide, this part of the claims have been taken into account for the definition of the peptide according to claim 12. Nevertheless the wording "comprising" does not limit the scope of the claims to the specific peptide seq.ID NO:6, but covers also larger amino acid sequences.

2.4 The same interpretation as for claim 12 applies for the subject-matter of claims 13-15,19-21 of the application.

3 **Novelty** (Art. 33(2) PCT)

3.1 The application discloses the identification of a tumour associated antigen for colorectal designated COA-1 having aa sequence ID NO:2. The immunogenic peptide, identified by seq.ID NO 6 (aa 372-385 of COA-1) is expressed in association with HLA class II molecules and elicit a T cell mediated immune response.

3.2 D2 reviews tumour antigens known to be relevant to colorectal cancer and which are recognized by T-cells and antibodies (see pg.184 3rd paragraph - pg.187 3rd paragraph). T-cell antigens may provide useful targets to develop immunotherapeutic strategies to treat cancer (see pg.182 5th paragraph - pg.183 4th paragraph). The subject-matter of claim 1 differs in that it refers to the use of a peptide comprising seq.ID NO 6. In the light of the available prior art the subject-matter of independent claim 1 is new (Art.33(2) PCT).

3.3 The subject-matter of independent claims 15,21,25,27-29 and dependent claims 2-10,16-18,22-24,26 is also new in the light of the available prior art.

3.4 D3 discloses seq.ID NO: 15 (pg.18/89) having 100% identity with seq.ID NO:2 of the application, the corresponding polynucleotide sequence is identified as seq.ID NO:48 (see Table I). Cells expressing the protein and antibody binding thereto are claimed (see cl. 7,9-11). D3 is detrimental to the novelty of the subject-matter of independent claims 11-14,19 and 20.

4 **Inventive Step** (Art.33(3) PCT)

4.1 The subject-matter of independent claim 1 does not involve an inventive step in the sense of Art. 33(3) PCT in combination with lack of support (Art.6 PCT) and therefore the criteria of Art. 33(1) PCT are not met.

4.2 The peptide identified by seq.ID NO:6 is a T cell epitope recognised by the CD4+ cells. The application exemplifies the use of present peptide in combination / bound to an MHC class II molecule. Alternatively a fragment of the protein COA-1 having seq.ID NO:2 and identified as COA-1a (aa209-1318) is cotransfected with MHCII molecules and shown to be immunogenic. However, there is no evidence that the peptide having seq.ID NO:6 may rise an immunogenic immunoresponse administered as isolated peptide. Consequently present claim 1 lacks support. Moreover, since the application does not provide any evidence that the isolated peptide may work as an immunogen it doesn't solve the problem of the application and is not based on an inventive step according to Art.33(3) PCT.

5 The same arguments cited for claim 1 point 3.2 are valid, mutatis mutandis, for the subject-matter of independent claims 15,21,27,28 and dependent claims 2-7,16,29 which therefore are also not inventive (Art.33(3) PCT).

6 The subject-matter of claim 25 is not limited to the COA-1 epitope having seq.ID NO:6 but covers also other epitopes than the one specifically disclosed in the application. Consequently the claim lacks support (Art.6 PCT) over its broad scope and disclosure (Art. 5 PCT), since the application does not provide any alternative epitope which may be used for stimulating immunity to colorectal cancer. As a consequence the claim is also not based on an inventive step since the claim covers also epitopes which do not solve the problem of the application Art.33(3) PCT.

6.1 The same arguments cited for claim 25 are valid, mutatis mutandis, for dependent claim 26 of the application.

7 The subject-matter of dependent claim 8 is based on an inventive step according to Art.33(3) PCT in the light of the available prior art. The features distinguishing the subject-matter of claim 8 from the closest prior art D2 and D3, namely the use of a peptide having seq.ID NO:6 in association with sympathetic MHC class II molecules as immunogen to stimulate an immune response against colorectal cancer and melanoma cells, cannot be derived in an obvious way from these documents. Consequently the use according to claim 8 is based on an inventive concept (Art.33(3) PCT).

7.1 Accordingly, the subject-matter of claims 9-10 comprising the subject-matter of claim 8

is also based on an inventive step (Art.33(3) PCT).

8 The subject-matter of dependent claims 17,18,22-24 is also based on an inventive concept (Art.33(3) PCT), the reason being similar as for claim 8. None of the available prior art documents, either if taken alone or in any combination, seems to anticipate or suggest the effective production of the vaccine according to claims 17,18 or the method to simulate an immune response according to claims 22-24.

9 For the assessment of the present claims 21-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

MACCALLI CRISTINA ET AL: "Identification of a colorectal tumor-associated antigen (COA-1) recognized by CD4+ T lymphocytes." CANCER RESEARCH, vol. 63, no. 20, 15 October 2003 (2003-10-15), pages 6735-6743 ISSN: 0008-5472

Re Item VII
Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2 and D3 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII
Certain observations on the international application

In claim 16 reference to claim 16 should probably read claim 15.